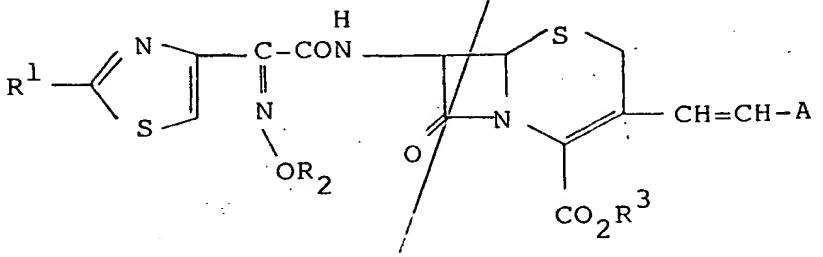
769746
Htsumi
8/22/85

What we claim is:

1. A cephalosporin compound of the general formula (I)



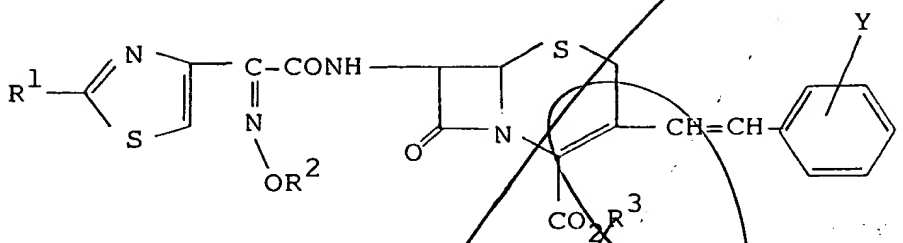
(I)

wherein R^1 is an amino group or a protected amino group; R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group; R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group; A is an unsubstituted or substituted phenyl group, an unsubstituted or substituted furyl group, an unsubstituted or substituted thiazolyl group or an unsubstituted or substituted 3-lower-alkylthiazolio group, and a pharmaceutically acceptable salt or ester of said cephalosporin compound.

Jap. priority 9/7/84 - 7/18/85

544/22, 27
514/202, 206

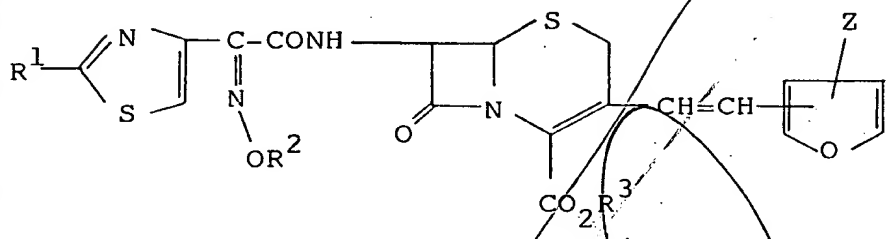
2. A cephalosporin compound as claimed in Claim 1 which is of the ~~general~~ formula (Ia)



(Ia)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and Y is a hydrogen atom, a lower alkyl group, a lower ~~alkoxyl~~ alkoxy group or a halogen atom.

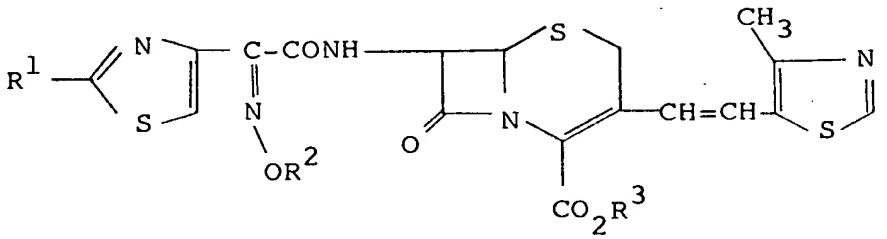
3. A cephalosporin compound as claimed in Claim 1 which is of the ~~general~~ formula (Ib)



(Ib)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, Z is a hydrogen atom, nitro group or a halogen atom.

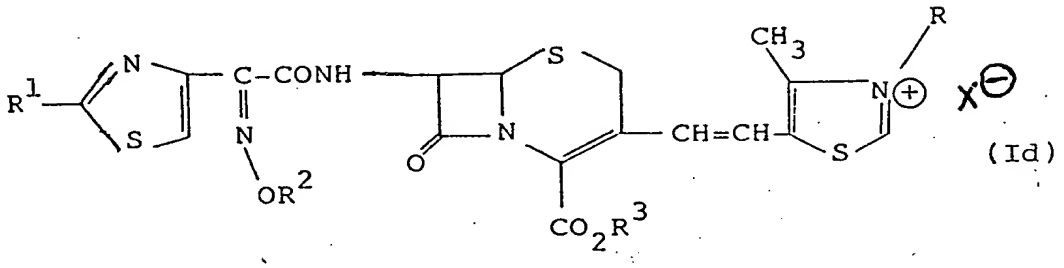
4. A cephalosporin compound as claimed in Claim 1 which is of the ~~general~~ formula (Ic)



(Ic)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

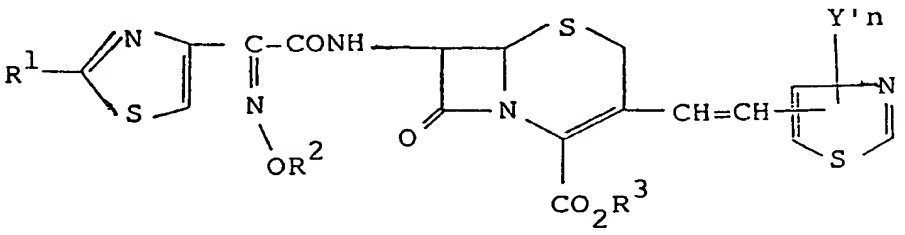
~~5.~~ A cephalosporin compound as claimed in claim 1 which is of the ~~general~~ formula (Id)



(Id)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1-C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, ~~and~~ R is a lower alkyl group, ~~and X is a halide~~

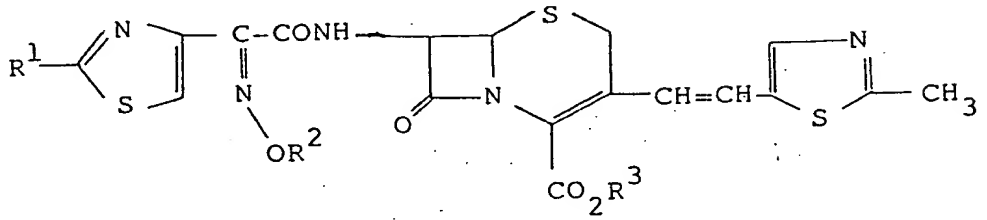
~~6.~~ A cephalosporin compound as claimed in claim 1 which is of the ~~general~~ formula (Ie)



(Ie)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1 - C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and Y' is a hydrogen atom or a halogen atom, and n is a whole number of 1 or 2.

55. A cephalosporin compound as claimed in claim 1 which is of the ~~general~~ formula (If)



(If)

wherein R^1 is an amino group or a protected amino group, R^2 is a lower (C_1 - C_6) alkyl group, a carboxymethyl group or a protected carboxymethyl group, and R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group.

56. A compound as claimed in claims 1 ~~to 7~~ in which R^1 is an amino group, R^2 is a methyl group or a carboxymethyl group, and R^3 is sodium atom, benzhydryl group, p-methoxybenzyl group, diphenylmethyl group, pivaloyloxymethyl group or (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl group.

9. A compound as claimed in Claim 1 which is selected from:-

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-(2-phenylvinyl)-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its trifluoroacetate; and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(o-fluorophenyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its ~~trifluoroacetate~~ acid addition salt with trifluoroacetic acid.

10. A compound as claimed in Claim 1 which is selected from:-

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its sodium salt;and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(5-nitro-2-furyl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its sodium salt.

17. A compound as claimed in claim 1 which is selected from the group consisting of

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-2-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer);

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-4-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) and its sodium salt and its pivaloyloxymethyl ester; and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(thiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), its sodium salt, and its pivaloyloxymethyl ester.

12. A compound as claimed in claim 1 which is selected from: from the group consisting of

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cepehm-4-carboxylic acid (cyn-isomer, trans-isomer, or cyn-isomer, cis-isomer), its sodium salt, its trifluoroacetate, its pivaloyloxymethyl ester, and its (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl ester;

7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl) acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) and its acid addition salt with trifluoroacetic acid ~~trifluoroacetate~~;

7-[2-t-butoxycarbonylmethoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl) vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer); and

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(2-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer), its sodium salt, its acid addition salt with trifluoroacetic acid ~~trifluoroacetate~~, and its (5-methyl-2-oxo-1,3-dioxolene-4-yl)-methyl ester.

9. A compound as claimed in claim 1 which is selected from the group consisting of

7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-chlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), its sodium salt and its pivaloyloxymethyl ester; and

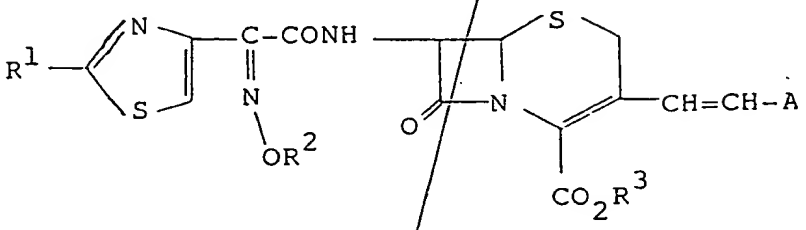
7-[2-methoxyimino-2-(2-amino-thiazol-4-yl)acetamido]-3-[2-(2,4-dichlorothiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer), its sodium salt and its pivaloyloxymethyl ester.

10. A compound as claimed in claim 1 which is 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(3,4-dimethyl-5-thiazolio)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, trans-isomer, or syn-isomer, cis-isomer) iodide or its acid addition salt with trifluoroacetic acid.

11. 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) sodium salt.

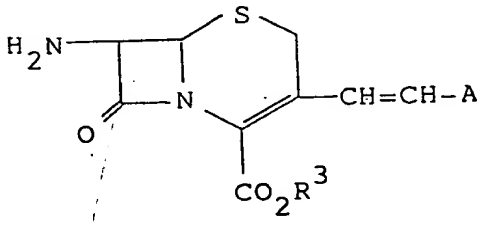
12. 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer) pivaloyloxymethyl ester.

17. A process for the production of a cepahlosporin compound of the general formula (I)



(I)

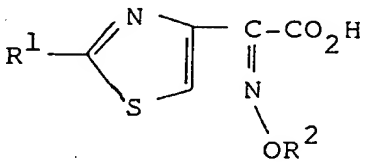
wherein R^1 is an amino group or a protected amino group, R^2 is a lower alkyl group, a carboxymethyl group or a protected carboxymethyl group, R^3 is a hydrogen atom, a salt-forming cation or a carboxyl-protecting group, and A is an unsubstituted or substituted phenyl group, an unsubstituted or substituted furyl group or an unsubstituted or substituted thiazolyl group or an unsubstituted or substituted 3-lower-alkylthiazolio group, characterized in that the process comprises reacting a 7-aminocephalosporanic acid compound of the general formula (II)



(II)

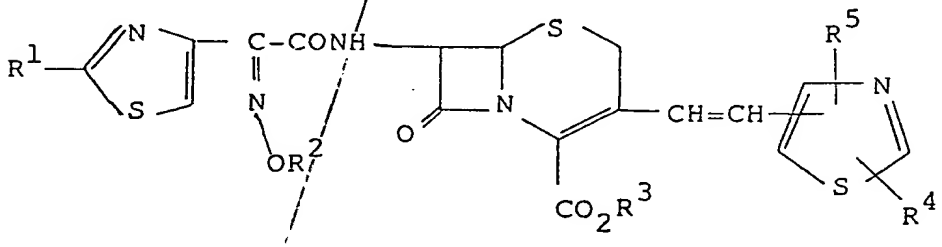
wherein R^3 and A are as defined above, or a functional equivalent thereof (including a reactive derivative at the amino group of the compound of the formula (II) and a salt

of the compound of the formula (II)), with a 2-(2-amino-thiazol-4-yl)-2-alkoxyimino-acetic acid compound of the formula (III)



(III)

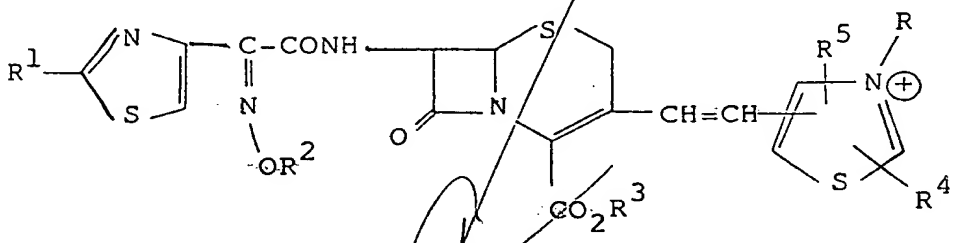
wherein R^1 and R^2 are as defined above, or a functional equivalent thereof (including a reactive acid derivative of the compound of the formula (III)) in an unreactive solvent at a temperature of not higher than the boiling temperature of the solvent used, to produce the compound of the formula (I), and then, if desired, where the product compound of the formula (I) as produced is such one as shown by the formula (I")



(I")

wherein R^1, R^2 and R^3 are as defined above, and R^4 and R^5 are the same or different and each are a hydrogen atom, a lower alkyl group or a halogen atom, alkylating the 3-nitrogen atom of the thiazolyl group of the compound

of the formula (I") by reacting with an alkyl halide of the formula RX wherein R is a lower alkyl group and X is a halogen atom, or a mono- or di-lower-alkyl sulfate or a lower alkyl lower-alkanesulfonate, to produce the compound of the formula (I"')



(I"')

wherein R^1, R^2, R^3, R^4 and R^5 are as defined above and R is corresponding to the lower alkyl group of the alkyl halide or the mono- or di-lower-alkyl sulfate or the lower alkyl lower-alkanesulfonate employed, and further, if desired, removing the remaining amino-protecting group and the remaining carboxyl-protecting group from the product compound of the formula (I) or of the formula (I"').

18. A pharmaceutical, antibacterial composition which comprises an antibacterially effective amount of the compound of the formula (I) as defined in claim 1 or the compound of the formula (Ia) to (If) as defined in any one of claims 2 to 5 or a pharmaceutically acceptable salt or ester thereof, as the active ingredient, in combination with a pharmaceutically acceptable carrier for the active ingredient.